

Comparison of the effects of isoflurane versus propofol-remifentanyl anesthesia on oxygen delivery during thoracoscopic lung lobectomy with one-lung ventilation in dogs

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This study compared effects of isoflurane inhalation (ISO) and propofol-remifentanyl combined total intravenous anesthesia (TIVA) on oxygenation during thoracoscopic lung lobectomy with 30-min one-lung ventilation (1LV). Thoracoscopic right middle lung lobectomy was performed in ten dogs divided into ISO and TIVA groups, and cardiopulmonary parameters were measured with blood gas analysis. Throughout the study, isoflurane was inhaled up to 1.5%, and the infusion rates of propofol and remifentanyl were 0.2 to 0.4 mg/kg/min and 6 to 11 μ g/kg/h, respectively. Cardiac index was not affected in the ISO group, but it increased during 1LV in the TIVA group. There were significant alterations in arterial oxygen pressure, arterial oxygen saturation, oxygen content, and shunt fraction associated with 1LV in each group. However, oxygen delivery did not decrease significantly due to open chest condition, 1LV, or surgical maneuver in either group, rather it increased during 1LV in the TIVA group. All parameters showed no significant difference between groups. Pulmonary vascular resistant index was unaffected in both groups, and there was no difference between groups except in re-ventilation phase. Accordingly, the effect of both anesthetic regimens on oxygenation was not different between groups and can be used with short-term 1LV for thoracoscopic lung lobectomy in dogs.

Keywords: dogs, isoflurane, one-lung ventilation, propofol-remifentanyl, thoracoscopic lung lobectomy

Introduction

As the field of minimally invasive surgery has been expanding in veterinary medicine, one-lung ventilation (1LV) is often accompanied in thoracoscopic lung surgery to facilitate motionless surgical approach with a benefit of optimal hilar visualization. During 1LV, however, collapse of the operated lung area blocks its ventilation completely, and there is a potential risk for considerable intrapulmonary right to left shunt of deoxygenated blood through the non-ventilated lung [15,16]. This theoretical ventilation-perfusion (V/Q) mismatch may result in hypoxemia and decreased oxygen saturation [2,15,16,18,28,30,31].

Hypoxic pulmonary vasoconstriction (HPV), a critical physiologic homeostatic mechanism, is activated in hypoxic condition, and pulmonary blood flow is diverted away from collapsed, hypoxic areas to better-oxygenated areas of the pulmonary vascular bed to match regional ventilation and perfusion [18,19,31]. This phenomenon decreases shunt fraction

and accordingly improves patients' oxygenation [25,27]. In clinic, most indications of lung lobectomy are in pathologic status of impaired oxygenation inducing poor alveolar distension-contraction such as pulmonary abscess, bullous emphysema, consolidation, neoplasia, or lung lobe torsion [22]. Associated hypoventilation, V/Q mismatching, shunt fraction, and dead space may deteriorate hypoxemia and hemoglobin desaturation. Moreover, 1LV in these patients might induce further risk potential with an artificially increased shunt fraction [15]. Under such conditions, attenuation of HPV could result in fatal intraoperative hypoxemia [2,3,6,18,27].

In general, it has been accepted that volatile anesthetics are known to inhibit HPV with a vasodilative effect counteracting the protective mechanism of HPV, while intravenous anesthetics do not depress HPV [7,25,27]. However, various authors have reported a variety of results, and there is no consensus currently [5,10,32]. According to previous reports, *in vitro* study in rat lung showed a negative effect with a median effective dose (ED50) of 0.6 minimum alveolar concentration (MAC)

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isoflurane inhalation [20], and *in vivo* study in chloralose-based intravenous anesthetized rabbit with 1LV reported increased regional blood flow to non-ventilated lung fields after conversion to 1.5% (0.75 MAC) isoflurane inhalation [7]. In human medicine, propofol improved oxygenation and shunt fraction during 1LV in an open chest condition for esophageal surgery compared with isoflurane and sevoflurane [1], and a three-fold greater shunt fraction with isoflurane compared with propofol was also reported [12]. On the other hand, a neutral to weak inhibitive action on HPV was observed with modern inhalants of isoflurane, sevoflurane, and desflurane in human medicine [4,18,27,31], whereas a total intravenous anesthesia (TIVA) of propofol-alfentanil combination in another human study did not decrease the risk of hypoxemia compared with 1 MAC isoflurane during 30-minute 1LV [26].

These results are inconsistent and depend on conditions of the study such as method of induction of hypoxic condition (hypoxic gas inhalation vs. 1LV), assessment of HPV (arterial blood gas analysis, pulmonary arterial catheterization, colored microsphere technique), type and dose of anesthetics, experimental animals, or *in vivo* vs. *in vitro* study [5,10,32]. Moreover, some studies excluded surgical maneuver and evaluated only under 1LV [3,14,17]. Consequently, it is inappropriate to compare results among studies, thus effects under real surgical condition remain unpredictable in dogs.

Considering these aspects, this study investigated the effects of two anesthetic regimens, isoflurane inhalation and propofol-remifentanyl combined TIVA, on HPV and oxygenation during thoracoscopic lung lobectomy with 1LV in Beagle dogs. The aims of this study were (1) to evaluate the effect of each anesthetic encountered during the overall steps of thoracoscopic lung lobectomy with 1LV, and (2) to determine differences between the two anesthetic groups.

Materials and Methods

Experimental animals

This study was performed under the guidance of the Chungnam National University Institutional Animal Care and Use Committees (CNU-00413). Ten 3-year-old, purpose-bred intact male Beagle dogs weighing 8.88 ± 0.75 kg (range, 8.0–10.0 kg; body condition score, 4/9–6/9) were included. All dogs were clinically healthy based on physical examination, complete blood count, serum biochemistry, electrolytes panel, and thoracic radiography. The dogs were randomly allocated into one of two groups of anesthetic regimens (isoflurane inhalation, ISO group; propofol-remifentanyl combined TIVA, TIVA group).

Anesthetic regimen

All dogs were oxygenated for 5 min prior to anesthetic induction. Normal saline was administered at 10 mL/kg/h. Glycopyrrolate (Mobinul, 0.011 mg/kg intravenous [IV];

Myungmoon Pharm, Korea) and diazepam (Diazepam, 0.1 mg/kg IV; Samjin Pharm, Korea) were used in the premedication of each dog. Anesthesia in five dogs (ISO group) was induced with propofol (Provive, 4 mg/kg IV; Myungmoon Pharm) and maintained with isoflurane (up to 2%, 1.5 MAC) after endotracheal intubation. In the other five dogs (TIVA group), propofol and remifentanyl (Ultiva; GlaxoSmithKline, UK) were administered for induction (4 mg/kg IV, 4 µg/kg IV) and infused for maintenance (up to 0.6 mg/kg/min constant rate infusion [CRI] and 6–20 µg/kg/h CRI) after endotracheal intubation. Rates of inhalation and infusion were controlled in response to patient monitoring parameters and recorded. Meloxicam (Metacam, 0.2 mg/kg IV; Boehringer Ingelheim Vetmedica, Germany) was administered immediately prior to anesthetic induction, and pure oxygen ($FiO_2 = 1$) was used throughout the procedure.

Anesthetic phases

Total anesthetic duration was divided into the following five phases according to the surgical process. (A) Pre: after anesthetic induction, two-lung ventilation with a closed chest, 10 min; (B) O2LV: after portal placements, two-lung ventilation with open chest, 20 min; (C) O1LV: after bronchial block, 1LV with open chest, 20 min; (D) LOBEC: thoracoscopic right middle lung lobectomy under 1LV, 10 min; and (E) REVENT: re-ventilation and expansion of the collapsed lung, 5 min. Each dog served as its own control. The durations of total anesthesia and 1LV (phase O1LV and LOBEC) were 65 min and 30 min, respectively.

In phase Pre, all dogs were placed in left lateral recumbency, and the right hemithorax was surgically prepped. The dorsal pedal artery was catheterized for systemic blood pressure monitoring and arterial blood sampling. A pulmonary artery catheter (Swan Ganz Catheter, 132F5, 110 cm; Edwards Lifesciences, USA) was introduced through the right external jugular vein using the Seldinger technique with characteristic monitoring pressure tracking to measure the pulmonary arterial pressure and cardiac output (CO) and to obtain mixed venous blood sample. Atracurium besylate (Atra, 0.2 mg/kg IV; Hana Pharm, Korea) was administered and the lungs were mechanically ventilated with a volume- and time-controlled ventilator after spontaneous respiration disappeared; Royal 77 (Royal Medical, Korea), tidal volume = 15 mL/kg, respiratory rate = 20 breaths/min, I/E ratio = 1:2, peak inspiratory pressure limit = 20 cmH₂O.

During phase O2LV, an open chest condition was obtained by taking an 8–6–5 intercostal approach with three soft threaded trocars (Thoracoport; Covidien, USA) as described previously [23]. Three openings were created for the 5 mm telescope, 12 mm stapler and specimen retrieval pouch, and 5 mm grasper, respectively.

Phase O1LV followed. 1LV was initiated with an endobronchial

blocker (Arndt Endobronchial Blocker Set, 5 Fr; Cook Critical Care, USA) occluding a main bronchial opening to the entire right lung field with guidance via a fiber-optic bronchoscope (EPK-700; Pentax Medical, Japan). Tidal volume was reduced by half of baseline during the O1LV and LOBEC phases. Each dog was vigilantly monitored, and the atelectasis of the right lung field was confirmed via thoracoscopy. Dislodging of the endobronchial blocker was monitored also.

In the LOBEC phase, thoracoscopic right middle lung lobectomy was performed with an endoscopic stapler and the resected lung lobe was retrieved with a specimen retrieval pouch. The surgical field was re-explored for hemorrhage, air leakage, or pedicle tearing.

In the REVENT phase, the collapsed lung lobes were re-expanded 10 times after the deflation of the endobronchial blocker by applying 5 cmH₂O positive end-expiratory pressure ventilation with 20 cmH₂O peak inspiratory pressure. The tidal volume restored to baseline, and ventilation was continued for additional 5 min.

After termination of all phases, dogs were humanely euthanized under anesthesia.

Evaluation

Patient monitoring included electrocardiogram, heart rate (HR), respiratory rate, capnogram, end-tidal carbon dioxide concentration, tidal volume, rectal temperature, core temperature, arterial blood pressure (systolic [SAP], mean [MAP], and diastolic), and pulse oximetry (SpO₂). These parameters were monitored and recorded by using a Datex S/5 system (Datex Ohmeda, Finland).

Hemodynamic changes, pulmonary arterial pressures (systolic, mean [MPAP], diastolic, and wedge [PAWP]) and CO with a thermodilution technique were measured and recorded at the following times of each phase: Pre-10 min (PRE), O2LV-20 min, O1LV-10 min, O1LV-20 min, LOBEC-10 min (LOBEC), and REVENT-5 min (REVENT). The mean value of three consecutive CO measurements was used for each datum. Arterial and mixed venous blood samples were collected anaerobically and analyzed (i-STAT Portable Clinical Analyzer; Heska, USA) simultaneously. Data were calculated using following standard formulae (Table 1); cardiac index (CI), shunt fraction (Q_s/Q_t), arterial oxygen content (CaO₂), oxygen delivery index (DO₂I), pulmonary vascular resistance index (PVRI).

Statistical analysis

All continuous variable data are presented as mean ± SD values. Normality of data distribution was examined by the Shapiro-Wilk test, and non-parametric methods were selected for non-normal distributions. For a comparison among all phases in each group, data were analyzed using Friedman's test which is related to non-parametric ANOVA with repeated

measures, and further multiple comparisons were performed with a Wilcoxon signed rank test when any significant difference was identified ($p < 0.05$). For differences between two independent groups in the same phase, data were compared by using the Mann-Whitney test. All analyses were performed with IBM SPSS Statistics (ver. 21.0; IBM, USA) and $p < 0.05$ was considered to indicate a significant difference.

Results

The anesthetic concentrations for maintenance were lower than that of the pre-planned protocol. In the ISO group, isoflurane was inhaled up to 1.5%, which was equivalent to approximately 1.125 MAC in dogs. In the TIVA group, the range of infusion rates of propofol and remifentanyl were 0.2 to 0.4 mg/kg/min and 6 to 11 µg/kg/h, respectively.

Intraoperative blood gas analysis and cardiopulmonary variable data at every assessment time in each group are shown in Table 2. HR in the ISO group significantly decreased after 1LV, while there was no significant difference among phases in the TIVA group or between the two groups. SAP and MAP increased with open chest and 1LV but it was not significantly different among phases in each group. In the REVENT phase, SAP ($p = 0.032$) and MAP ($p = 0.016$) in the ISO group were lower than that of the TIVA group.

CI levels did not differ between groups or among the phases in the ISO group; however, it was significantly higher in phases of O1LV-20 and LOBEC than that of PRE and O2LV-20 phases in TIVA. During 1LV, Q_s/Q_t increased significantly in each group, but there was no significant difference between groups. As for PaCO₂ and pH, PaCO₂ increased while pH decreased

Table 1. Equations of hemodynamic parameters [13]

Hemodynamic calculations
$CI = \frac{CO}{\text{body surface area}} \text{ (L min}^{-1} \text{ m}^{-2}\text{)}$
$CaO_2 = (1.36 \times Hb \times SaO_2) + 0.003 \times PaO_2 \text{ (mL dL}^{-1}\text{)}$
$PVRI = \frac{(MPAP - PAWP)}{CI} \times 80 \text{ (dynes sec cm}^{-5} \text{ m}^{-2}\text{)}$
$DO_2I = CaO_2 \times CI \times 10 \text{ (mL min}^{-1} \text{ m}^{-2}\text{)}$
$Q_s/Q_t = \frac{Cc'O_2^* - CaO_2}{Cc'O_2 - CvO_2^\dagger} \times 100 \text{ (\%)}$

CI, cardiac index; CO, cardiac output; CaO₂, arterial oxygen content; Hb, hemoglobin; SaO₂, arterial oxygen saturation; PaO₂, arterial oxygen pressure; PVRI, pulmonary vascular resistance index; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; DO₂I, oxygen delivery index; Q_s/Q_t, shunt fraction. *Cc'O₂ (pulmonary capillary blood oxygen content) = (1.36 × Hb × 100/100) + 0.003 × P_AO₂[‡] (mL dL⁻¹). †CvO₂ (mixed venous oxygen content) = (1.36 × Hb × SvO₂) + 0.003 × PvO₂ (mixed venous oxygen pressure) (mL dL⁻¹). ‡P_AO₂ (alveolar oxygen tension) = [FiO₂ × (P_B - P_{H₂O})] - 1.2 PaCO₂ (mmHg).

Table 2. Changes of hemodynamic and cardiopulmonary parameters in the ISO and TIVA groups during thoracoscopic right middle lung lobectomy with 1LV in dogs

Variable	Group	Phase						p value*
		Pre	O2LV-20	O1LV-10	O1LV-20	LOBEC	REVENT	
HR (beats/min)	ISO	139.8 ± 15.0	125.4 ± 17.4	107.2 ± 15.25 ^{ab}	111.6 ± 7.7 ^{ab}	107.6 ± 11.7 ^{ab}	116.6 ± 14.4 ^{ae}	0.003
	TIVA	115.2 ± 34.7	116.4 ± 40.1	121.0 ± 23.4	132.0 ± 25.1	123.4 ± 20.4	107.0 ± 32.6	0.746
SAP (mmHg)	ISO	84.4 ± 20.8	92.6 ± 21.7	85.2 ± 11.3	94.0 ± 17.5	85.2 ± 14.1	85.0 ± 11.5 [†]	0.449
	TIVA	103.8 ± 13.3	110.2 ± 8.4	110.0 ± 19.3	110.4 ± 21.2	103.2 ± 21.4	112.6 ± 16.3	0.621
MAP (mmHg)	ISO	71.0 ± 16.5	81.4 ± 16.4	72.2 ± 10.3	77.4 ± 15.3	72.4 ± 15.7	56.8 ± 22.3 [†]	0.111
	TIVA	86.8 ± 15.1	91.8 ± 12.5	90.2 ± 19.2	93.4 ± 23.3	87.0 ± 21.0	94.0 ± 17.6	0.917
CI (L min ⁻¹ m ⁻²)	ISO	5.94 ± 1.59	5.69 ± 1.50	5.20 ± 0.55	5.33 ± 0.75	5.18 ± 1.19	5.56 ± 1.00	0.858
	TIVA	4.60 ± 0.61	4.88 ± 0.93	5.66 ± 1.20	6.36 ± 0.78 ^{abc}	6.50 ± 1.86 ^{ab}	5.08 ± 1.54 ^e	0.012
Q ₂ /Q ₁ (%)	ISO	25.7 ± 22.1	25.1 ± 14.9	62.6 ± 11.3 ^b	59.5 ± 19.1 ^{ab}	51.9 ± 20.9	36.3 ± 17.8 ^{cde}	0.010
	TIVA	30.2 ± 19.7	52.9 ± 30.3	64.0 ± 12.0 ^a	73.6 ± 14.1 ^a	71.4 ± 19.4 ^a	53.9 ± 21.0 ^{ad}	0.024
PaCO ₂ (mmHg)	ISO	56.1 ± 7.6	70.6 ± 15.0	91.4 ± 12.1 ^a	93.0 ± 22.3 ^a	96.7 ± 20.6 ^a	66.4 ± 21.9 ^{cde}	0.006
	TIVA	60.0 ± 8.9	57.5 ± 9.6	73.8 ± 11.9 ^{ab}	78.2 ± 13.7 ^b	94.5 ± 13.8 ^{abcd}	62.0 ± 11.6 ^{ce}	0.001
pH	ISO	7.27 ± 0.02	7.17 ± 0.08	7.04 ± 0.03 ^{ab†}	7.03 ± 0.05 ^a	7.01 ± 0.07 ^{ab}	7.17 ± 0.10 ^{cde}	0.002
	TIVA	7.25 ± 0.05	7.25 ± 0.06	7.14 ± 0.07 ^{ab}	7.11 ± 0.07 ^{ab}	7.04 ± 0.06 ^{abcd}	7.22 ± 0.08 ^{cde}	0.000
SpO ₂ (%)	ISO	97.2 ± 2.4	95.0 ± 3.5	91.8 ± 4.1 ^a	91.2 ± 5.0 ^a	92.2 ± 4.3 ^a	96.0 ± 1.9 ^{cd}	0.002
	TIVA	96.4 ± 1.5	96.4 ± 1.8	92.6 ± 5.3	92.4 ± 3.6 ^{ab}	91.0 ± 4.7 ^{ab}	95.4 ± 2.9 ^{dle}	0.002
PaO ₂ (mmHg)	ISO	572.0 ± 44.1	518.0 ± 64.9	158.8 ± 99.1 ^{ab}	130.8 ± 46.2 ^{ab}	193.4 ± 156.8 ^{ad}	422.0 ± 105.7 ^{acde}	0.001
	TIVA	590.6 ± 20.7	533.0 ± 37.0	190.0 ± 65.3 ^{ab}	126.6 ± 17.4 ^{abc}	128.2 ± 19.5 ^{ab}	463.0 ± 90.2 ^{acde}	0.000
SaO ₂ (%)	ISO	100	100	96.0 ± 3.1	95.2 ± 3.7 ^{ab}	95.4 ± 4.2 ^{ab}	100 ^{de}	0.001
	TIVA	100	100	96.8 ± 4.1	96.8 ± 4.1 ^{abe}	95.8 ± 1.8 ^{(a)(b)}	100 ^{d(e)}	0.001
CaO ₂ (mL/dL)	ISO	21.7 ± 3.7	21.5 ± 3.8	19.6 ± 3.2 ^{ab}	19.4 ± 3.3 ^{ab}	19.6 ± 3.0 ^{ab}	21.3 ± 3.7 ^{acde}	0.001
	TIVA	25.0 ± 2.8	24.8 ± 2.7	23.0 ± 2.5 ^{ab}	22.9 ± 2.6 ^{ab}	22.6 ± 2.7 ^{ab}	24.6 ± 2.6 ^{abde}	0.001
DO ₂ l (mL min ⁻¹ m ⁻²)	ISO	1,302.5 ± 482.5	1,241.5 ± 463.2	1,016.8 ± 174.5	1,037.4 ± 247.7	1,034.5 ± 357.5	1,186.3 ± 330.7	0.053
	TIVA	1,147.1 ± 196.2	1,220.0 ± 307.1	1,317.3 ± 348.3	1,460.8 ± 271.4 ^{ab}	1,475.0 ± 454.4 ^a	1,250.3 ± 408.2 ^e	0.040
MPAP (mmHg)	ISO	11.8 ± 1.8	15.0 ± 4.4 [‡]	15.4 ± 1.9	17.4 ± 2.3 [‡]	17.0 ± 1.4 ^(a)	14.8 ± 1.6 ^{(e)lde}	0.005
	TIVA	11.6 ± 2.1	12.6 ± 0.9	17.6 ± 2.9 ^{ab}	21.6 ± 7.7 ^{ab}	19.4 ± 3.6 ^{ab}	14.0 ± 2.4	0.001
PAWP (mmHg)	ISO	2.2 ± 1.8	6.2 ± 3.4 [‡]	6.6 ± 2.3 [‡]	8.0 ± 3.4 [‡]	8.2 ± 3.1 [‡]	6.2 ± 4.0	0.009
	TIVA	2.0 ± 1.9	3.8 ± 1.5	4.4 ± 2.3	5.8 ± 3.2	5.6 ± 2.9	3.0 ± 1.9	0.083
PVRI (dynes sec cm ⁻⁵ m ⁻²)	ISO	135.4 ± 41.9	125.7 ± 31.9	137.0 ± 42.5	144.6 ± 39.1	138.7 ± 44.0	123.1 ± 31.6 [†]	0.604
	TIVA	169.5 ± 34.5	150.0 ± 44.8	196.2 ± 66.0	202.0 ± 70.7	178.9 ± 46.7	173.7 ± 23.9	0.152

Data are presented as mean ± SD. ISO, isoflurane inhalation; TIVA, total intravenous anesthesia; HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; CI, cardiac index; Q₂/Q₁, shunt fraction; PaCO₂, arterial carbon dioxide pressure; pH, acidity; SpO₂, pulse oximetry; PaO₂, arterial oxygen pressure; SaO₂, arterial oxygen saturation; CaO₂, arterial oxygen content; DO₂l, oxygen delivery index; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVRI, pulmonary vascular resistance index; Pre, closed chest 2 lung ventilation; O2LV-20, 20 min after open chest 2 lung ventilation; O1LV-10, 10 min after open chest 1 lung ventilation; O1LV-20, 20 min after open chest 1 lung ventilation; LOBEC, thoracoscopic right middle lung lobectomy under 1 lung ventilation, 10 min; REVENT, 5 min after re-ventilation. † p value of Friedman's test comparing among phases within each group. ‡ Significantly different between groups (p < 0.05). Significantly different from †Pre, †O2LV-20, †O1LV-10, †O1LV-20, and †LOBEC (p < 0.05). Superscripts expressed as ^{a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z}. Indicate p values of 0.043, 0.042, 0.041, 0.039, respectively.

with 1LV significantly, but they restored in the REVENT phase. PaCO₂ was not different between groups, but a significantly lower pH level was identified in the ISO group than that of the TIVA group in O1LV-10 phase ($p = 0.008$).

Regarding intraoperative oxygenation, SpO₂, arterial oxygen pressure (PaO₂), arterial oxygen saturation (SaO₂), and CaO₂ in both groups decreased significantly during 1LV but restored in the REVENT phase to the level of PRE (SpO₂, SaO₂), O2LV-20 (PaO₂, CaO₂ in ISO), and O1LV-10 (CaO₂ in TIVA). DO₂I in the ISO group showed no significant change among phases although there was a tendency of decrease during 1LV. In the TIVA group, on the other hand, significantly higher DO₂I were identified in O1LV-20 and LOBEC phases than that in the PRE phase, and the level decreased in the REVENT phase. None of these 5 parameters showed a significant difference between the two groups.

There were significant increases of MPAP and PAWP in the ISO group and MPAP in the TIVA group during 1LV, but there was no difference between groups. PVRI values were not significantly different in either group and also between groups except in the REVENT phase ($p = 0.032$).

Discussion

This study attempted to answer the question of how we can reduce burden on canine patients for lung lobectomy while mitigating the risk of hypoxia. In lateral recumbency, an intercostal thoracotomy enables over-inflation of the non-dependent lung as the thoracic wall does not limit its expansion, while ventilation of the dependent lung is impaired because the loss of negative intra-thoracic pressure induces compression of the lower lung via the weight of the heart, mediastinum, and abdominal organs. However, lung perfusion is more concentrated on the dependent side due to the gravity [13,18], and these complicated conditions contribute to V/Q mismatch.

Contrary to the approach in thoracotomy, the thoracic wall is intact during thoracoscopy and it prevents the over-inflation of the non-dependent lung. Therefore, a higher proportion of ventilation occurs in the dependent lung, resulting in a smaller Q_s/Q_t and a lower reduction in PaO₂, SaO₂, and CaO₂. Previously, a 19% reduction in PaO₂ with unaffected SaO₂ was reported during thoracoscopic cannulae placement, whereas a 29% to 39% reduction in PaO₂ accompanied by a significant decrease in SaO₂ was induced by intercostal thoracotomy [13].

Thus, we selected a thoracoscopic procedure for lung lobectomy and included 1LV, which could be decisive in some cases. With 1LV, the non-dependent lung is excluded from the ventilatory circuit completely, thus it becomes a true shunt [18]. In this scenario, ventilation is restricted to the dependent lung, although Q_s/Q_t increases. At this moment, a concentrated blood flow to the region where the gas exchange occurs is key to improve patients' oxygenation; this is why HPV should be

optimized with 1LV. HPV can reduce shunt flow through the operative lung by 40% approximately [18].

The mechanism of HPV has not been fully described. It is thought of as a local constriction of vascular smooth muscle in the pulmonary circulation in response to regional hypoxia; an initial decrease in alveolar oxygen pressure (P_AO₂) followed by a mixed venous oxygen pressure (P_VO₂) [18,19,33]. HPV occurs within a few seconds and reaches an initial peak in 15 to 20 min (phase 1) and can be prolonged for 2 to 4 h (phase 2) as a peak effect [18,19]. HPV may be assessed with oxygenation and PVRI indirectly or via a microsphere technique to measure the direct regional blood flow [3,17,18]. The net effect of the hemodynamic and respiratory changes of any treatment can be assessed through the evaluation of DO₂I [14]. The incidence of hypoxemia associated with 1LV was recently reported as 5%; that rate has decreased from 25% in the 1970s owing to improvement of lung isolation technique, anesthetic agents, and better comprehension of the physiology of 1LV [19].

HPV is influenced by several factors such as general anesthesia, surgical manipulation, trauma, size of the hypoxic segment, intensity of the hypoxic stimulus, or temperature and age [2,3,6,18,27]. Whereas surgical manipulation in lateral recumbency reduces blood flow to the non-dependent lung with gravity passively [18], the anesthetic agents, muscle paralysis and mechanical ventilation, lateral recumbency, and atelectasis can deteriorate Q_s/Q_t, V/Q mismatch, and arterial hypoxemia [13]. However, these changes might be inevitable during practical surgery, and there is a need to evaluate anesthetic effects under the actual surgical conditions. This study was conducted under the most extreme hypoxic condition of left-sided 1LV, which excludes the right lung area that occupies 58% of the total lung volume [8]. Efforts were focused on maintaining anesthetic techniques and surgical procedures relevant to real clinical practice. The experimental phases followed the same courses as those of thoracoscopic lung lobectomy, and anesthetic depth was controlled to be just suitable for surgery.

In this study, obvious impairments in gas exchange were induced during 30 min 1LV in both anesthetic groups. There were significant decreases in PaO₂, SaO₂, and CaO₂, whereas PaCO₂ increased and respiratory acidosis was intensified. However, neither hypoxemia nor desaturation that were unacceptable (*i.e.*, PaO₂ < 60 mmHg, SpO₂ < 90, SaO₂ < 91% [9,29]) did not develop in either group. In addition, despite CaO₂ decreasing numerically during 1LV, it was relatively well maintained in all phases and in both groups within or over the normal range (16–20 mL/dL) [9]. Moreover, none of the assessment times showed significantly lower CaO₂ compared to that of the PRE phase.

When we consider the insignificant change in PVRI despite significant increases in MPAP or PAWP, as well as the unaffected oxygen delivery regardless of significantly increased

shunt fractions, neither anesthetic regimen in this study appeared sufficient to impair oxygenation. Q_s/Q_t increased significantly after initiation of 1LV in both groups but did not show a significant decrease until end of 30 min 1LV. Oxygen delivery was maintained regardless of any of open thorax, 1LV, or surgical maneuver, and it was not different between groups. This might be attributed to the high fraction of inspired oxygen ($FiO_2 = 1.0$) or low anesthetic concentration, and the latter could be a reflection of the characteristics of minimally invasive surgery; a smaller incision and less pain. It is also possible that the overall effects of complicated *in vivo* compensation mechanisms avoided hypoxemia in advance of HPV. The effects of HPV seem to be maximized in conditions of low P_{AO_2} from 25 to 50 mmHg, low V/Q with hypoxic lung area between 30% and 70%, and hyperthermia [19].

In several reports, HPV was reported to be decreased by volatile anesthetics under *in vitro* and *in vivo* conditions. The attenuation appeared in a dose-dependent manner, especially with old agents [5], and some authors suggested that the clinical relevance of this effect is negligible [18]. Suppressing effects of volatile anesthetics are more potent when the pulmonary vascular region of HPV is exposed through the alveolus rather than via mixed venous blood [19]. If 1LV is stable, the agent is delivered by mixed venous blood. The anesthetic concentration in this study was even lower than that in a previous study that reported non-affected DO_2I by 1LV under 1.5 MAC isoflurane inhalation; in that study, oxygenation was evaluated in the same manner as in present study, but it was not accompanied by surgical procedure [14]. Although respiratory acidosis was more severe in the ISO group than in the TIVA group after initiation of 1LV, it might be less influential on HPV. As mentioned above, HPV is a response to the oxygen pressure (hypoxia) rather than that of carbon dioxide. Indeed, HPV is less associated with hypercapnia or respiratory acidosis but is attenuated by hypocapnia, instead [19].

During 1LV, CI increased significantly in the TIVA group, which is counter to the general characteristic of propofol anesthesia presenting a decrease in CO. It seemed to be associated with an increase in HR for a decrease in PaO_2 , although that change was insignificant. It is followed by an increase in DO_2I because DO_2I is determined by both CO and CaO_2 . Even though CaO_2 declined, the degree of change in CO was relatively greater than that of CaO_2 at the end of 1LV. Nevertheless, it did not result in a significant change in PVRI. On the other hand, in the ISO group, there was a significant decrease of HR after initiation of 1LV, which was accompanied by a non-significant decrease in CI and DO_2I . With significant increases in MPAP or both MPAP and PAWP associated with 1LV in both groups, PVRI values during the phases with 1LV were higher than those of the other phases in both groups, but the differences were not significant. Similarly, there was a tendency to higher values in the TIVA group than in the ISO

group in every phase, but there was no significant difference between two groups other than in the REVENT phase.

Previous canine studies with 1LV usually did not include surgical procedures [3,10,14,32]. Recent retrospective research in human medicine investigated during thoracic surgeries with 1LV but evaluated mainly only PaO_2 , blood pressure, or HR [5,24,27,29]. Our results are supported by these human studies, which concluded there were no significant differences in PaO_2 , MAP, or HR between propofol-based TIVA and volatile anesthetics using isoflurane [26,29] or sevoflurane [24]. Regarding thoracoscopic lung lobectomy in human medicine, a propofol-remifentanyl combination was suitable and did not alter PaO_2 [5,27], and one study reported that combination provided better oxygenation than a desflurane-remifentanyl combination [5]. A previous study on thoracoscopic subphrenic pericardiectomy with 1LV was performed under isoflurane inhalation (up to 2.0%) in normal dogs. The authors monitored only PaO_2 , $PaCO_2$, and SpO_2 and reported relatively acceptable ventilation and oxygenation, although they did report a significant decrease in PaO_2 during 1LV [21]. In another case report of thoracoscopic pericardial fenestration in a dog with a heart base tumor showed slight respiratory acidosis and considerable impairment in oxygenation parameters on arterial blood analysis; minimal PaO_2 was 96 mmHg at 170 min [2]. That study was performed under sevoflurane inhalation with 1LV excluding the right lung field as in the present study.

When interpreting our results, the following limitations should be considered. First, this study included a small number of healthy dogs, and there was a lack of data after anesthetic recovery when patients might be in unstable cardiovascular/hemodynamic status with reduced ability of compensation and impaired immunity. Further study of a large number of clinical patients with impaired gas exchange with long-term tracking after recovery from anesthesia is warranted. Second, the experimental conditions might be not controlled completely among phases with serial intervention of a surgical procedure. In addition, the concentration of anesthetics was not fixed, which was because the study was performed to act as a replication of real surgery. Third, the duration of 30 min 1LV could be too short to monitor the further effects of HPV, although it might be enough for the surgical procedure. According to a previous review, PaO_2 level reaches its lowest 20 to 30 min after 1LV and then increases gradually over the next 1 to 2 h [19]. Fourth, anesthesia and measurements were not carried out in a blind manner throughout the study, and the net effect of oxygenation was evaluated via an indirect method. Although a direct determination of blood flow with colored microsphere technique in pulmonary artery could provide further information on alteration in the distribution of blood flow at the level of capillaries in each phase, it was impractical to perform this technique in our clinic.

In summary, both 1.5% (1.125 MAC) isoflurane inhalation

anesthesia and propofol-remifentanyl combined TIVA did not affect patients' overall oxygenation throughout the thoracoscopic lung lobectomy procedure with 30-minute left-sided 1LV in dogs. Therefore, both anesthetic regimens can be used according to the surgeon's preference for thoracoscopic procedures with 1LV. However, observations of 1) severe hypercapnia and respiratory acidosis with 1LV in ISO group than TIVA group, 2) an increase in DO₂I with CI during 1LV in TIVA group, and 3) a highly maintained SAP and MAP in the TIVA group before end of the study should be considered during case selection. TIVA could be safer in patients with cardiovascular instability concerns. This study recommends vigilant anesthetic monitoring in patients with cardiopulmonary disease as significant alterations in gas exchange associated with 1LV were induced regardless of the anesthetic regimen. Normocapnia and normothermia should be maintained during surgery, as HPV could be attenuated by hypocapnia and hypothermia [19]. Life-threatening hypoxemia during 1LV should be prevented by checking for the location of endobronchial blockers or double lumen tubes, increasing FiO₂, applying 5 cmH₂O positive end-expiratory pressure, re-expansion of the non-ventilated lung, or by administration of respiratory stimulants such as almitrine [11,15,18].

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Conflict of Interest

The authors declare no conflicts of interest.

References

1. **Abe K, Shimizu T, Takashina M, Shiozaki H, Yoshiya I.** The effects of propofol, isoflurane, and sevoflurane on oxygenation and shunt fraction during one-lung ventilation. *Anesth Analg* 1998, **87**, 1164-1169.
2. **Bauquier SH, Culp WT, Lin RC, Larenza MP.** One-lung ventilation using a wire-guided endobronchial blocker for thoracoscopic pericardial fenestration in a dog. *Can Vet J* 2010, **51**, 1135-1138.
3. **Cantwell SL, Duke T, Walsh PJ, Remedios AM, Walker D, Ferguson JG.** One-lung versus two-lung ventilation in the closed-chest anesthetized dog: a comparison of cardiopulmonary parameters. *Vet Surg* 2000, **29**, 365-373.
4. **Carlsson AJ, Bindeslev L, Hedenstierna G.** Hypoxia-induced pulmonary vasoconstriction in the human lung. The effect of isoflurane anesthesia. *Anesthesiology* 1987, **66**, 312-316.
5. **Cho YJ, Kim TK, Hong DM, Seo JH, Bahk JH, Jeon Y.** Effect of desflurane-remifentanyl vs. Propofol-remifentanyl anesthesia on arterial oxygenation during one-lung ventilation for thoracoscopic surgery: a prospective randomized trial. *BMC Anesthesiol* 2017, **17**, 9.
6. **Fujiwara M, Abe K, Mashimo T.** The effect of positive end-expiratory pressure and continuous positive airway pressure on the oxygenation and shunt fraction during one-lung ventilation with propofol anesthesia. *J Clin Anesth* 2001, **13**, 473-477.
7. **Groh J, Kuhnle GE, Ney L, Sckell A, Goetz AE.** Effects of isoflurane on regional pulmonary blood flow during one-lung ventilation. *Br J Anaesth* 1995, **74**, 209-216.
8. **Hsia CC, Dane DM, Estrera AS, Wagner HE, Wagner PD, Johnson RL Jr.** Shifting sources of functional limitation following extensive (70%) lung resection. *J Appl Physiol* (1985) 2008, **104**, 1069-1079.
9. **Irizary R, Reiss A.** Beyond blood gases: making use of additional oxygenation parameters and plasma electrolytes in the emergency room. *Compend Contin Educ Vet* 2009, **31**, E1-5.
10. **Ishibe Y, Umeda T, Shiokawa Y, Izumi T, Nakamura M, Uno H, Suekane K.** [Evaluation of halothane induced HPV inhibition with analysis of pressure-flow curve]. *Masui* 1992, **41**, 586-594. Japanese.
11. **Karzai W, Schwarzkopf K.** Hypoxemia during one-lung ventilation: prediction, prevention, and treatment. *Anesthesiology* 2009, **110**, 1402-1411.
12. **Kellow NH, Scott AD, White SA, Feneck RO.** Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery. *Br J Anaesth* 1995, **75**, 578-582.
13. **Kudnig ST, Monnet E, Riquelme M, Gaynor JS, Corliss D, Salman MD.** Cardiopulmonary effects of thoracoscopy in anesthetized normal dogs. *Vet Anaesth Analg* 2004, **31**, 121-128.
14. **Kudnig ST, Monnet E, Riquelme M, Gaynor JS, Corliss D, Salman MD.** Effect of one-lung ventilation on oxygen delivery in anesthetized dogs with an open thoracic cavity. *Am J Vet Res* 2003, **64**, 443-448.
15. **Kudnig ST, Monnet E, Riquelme M, Gaynor JS, Corliss D, Salman MD.** Effect of positive end-expiratory pressure on oxygen delivery during 1-lung ventilation for thoracoscopy in normal dogs. *Vet Surg* 2006, **35**, 534-542.
16. **Lansdowne JL, Monnet E, Twedt DC, Dermell WS.** Thoracoscopic lung lobectomy for treatment of lung tumors in dogs. *Vet Surg* 2005, **34**, 530-535.
17. **Loeb V, Preussler NP, Gaser E, Schreiber T, Hueter L, Karzai W, Schubert H, Schwarzkopf K.** The effects of sevoflurane and propofol on oxygenation and lung perfusion during one-lung ventilation in an animal model. *Adv Clin Exp Med* 2011, **20**, 249-253.
18. **Lohser J.** Evidence-based management of one-lung ventilation. *Anesthesiol Clin* 2008, **26**, 241-272, v.
19. **Lumb AB, Slinger P.** Hypoxic pulmonary vasoconstriction: physiology and anesthetic implications. *Anesthesiology* 2015, **122**, 932-946.
20. **Marshall C, Lindgren L, Marshall BE.** Effects of halothane, enflurane, and isoflurane on hypoxic pulmonary vasoconstriction in rat lungs in vitro. *Anesthesiology* 1984, **60**, 304-308.
21. **Mayhew KN, Mayhew PD, Sorrell-Raschi L, Brown DC.**

- Thoracoscopic subphrenic pericardectomy using double-lumen endobronchial intubation for alternating one-lung ventilation. *Vet Surg* 2009, **38**, 961-966.
22. **Monnet E.** Lungs. In: Tobias KM, Johnston SA (eds.). *Veterinary Surgery: Small Animal*. pp. 1752-1768, Elsevier Saunders, St. Louis, 2012.
 23. **Park JY, Lee HB, Jeong SM.** Portal placement for thoracoscopic right middle lung lobectomy with one-lung ventilation in beagle dogs. *J Vet Clin* 2015, **32**, 9-15.
 24. **Pruszkowski O, Dalibon N, Moutafis M, Jugan E, Law-Koune JD, Laloë PA, Fischler M.** Effects of propofol vs sevoflurane on arterial oxygenation during one-lung ventilation. *Br J Anaesth* 2007, **98**, 539-544.
 25. **Purugganan RV.** Intravenous anesthesia for thoracic procedures. *Curr Opin Anaesthesiol* 2008, **21**, 1-7.
 26. **Reid CW, Slinger PD, Lenis S.** A comparison of the effects of propofol-alfentanil versus isoflurane anesthesia on arterial oxygenation during one-lung ventilation. *J Cardiothorac Vasc Anesth* 1996, **10**, 860-863.
 27. **Ryu CG, Min SW, Kim J, Han SH, Do SH, Kim CS.** Effect of remifentanyl on arterial oxygenation during one-lung ventilation. *J Int Med Res* 2010, **38**, 1749-1758.
 28. **Schilling T, Kozian A, Kretschmar M, Huth C, Welte T, Bühling F, Hedenstierna G, Hachenberg T.** Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. *Br J Anaesth* 2007, **99**, 368-375.
 29. **Sharifian Attar A, Tabari M, Rahnamazadeh M, Salehi M.** A comparison of effects of propofol and isoflurane on arterial oxygenation pressure, mean arterial pressure and heart rate variations following one-lung ventilation in thoracic surgeries. *Iran Red Crescent Med J* 2014, **16**, e15809.
 30. **Sugasawa Y, Yamaguchi K, Kumakura S, Murakami T, Suzuki K, Nagaoka I, Inada E.** Effects of sevoflurane and propofol on pulmonary inflammatory responses during lung resection. *J Anesth* 2012, **26**, 62-69.
 31. **Taleska G, Trajkovska T.** The effect of one lung ventilation on intrapulmonary shunt during different anesthetic techniques. In: Guerreiro Cardoso PF (ed.). *Topics in Thoracic Surgery*. Chapter. 3. InTech, Rijeka, 2012.
 32. **Uno H, Ishibe Y, Umeda T, Shiokawa Y, Izumi T, Tanaka K, Suekane K.** [Evaluation of inhibitory effect of isoflurane on the hypoxic pulmonary vasoconstriction response in dogs]. *Masui* 1994, **43**, 1288-1296. Japanese.
 33. **Weissmann N, Sommer N, Schermuly RI, Ghofrani HA, Seeger W, Grimminger F.** Oxygen sensors in hypoxic pulmonary vasoconstriction. *Cardiovasc Res* 2006, **71**, 620-629.